Montaner *et al.*, 2007). It would be interesting and important to determine whether Cv-pdg-NLS-TAT repaired this type of DNA damage as well. This enzyme may not have a direct effect on the repair of oxidative DNA damage, but it may contribute to an overall upregulation of repair mechanisms in the nuclear environment.

Because NMSCs continue to be a major health and economic issue, the development of new treatment and preventive modalities is crucial. In addition to standard recommendations such as sun avoidance and the application of sunscreen, there are promising treatments and preventive therapies on the horizon. Cv-pdg-NLS-TAT may be one such modality; future clinical studies will further define its efficacy and tolerability.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Peeling Skin Syndrome: Genetic Defects in Late Terminal Differentiation of the Epidermis

Paul E. Bowden[1]

In this issue, Israeli and colleagues confirm that homozygous mutations in corneodesmosin (CDSN) cause type B peeling skin syndrome (PSS), an autosomal recessive skin disorder. The deletion mutation described resulted in a frameshift, producing a downstream premature stop codon and early truncation of the protein. The recently described CDSN nonsense mutation in another PSS family also resulted in protein truncation and nonsense-mediated mRNA decay. Type B generalized PSS can now be clearly distinguished from acral PSS, caused by mutations in transglutaminase 5. This directly affects cornified envelope cross-linking rather than corneodesmosome adherence. These observations provide new insight into the molecular defects underlying two closely related forms of PSS.

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PSS

Peeling skin syndrome (PSS), first described in the early twentieth century (Fox, 1921), is a rare cutaneous genodermatosis that is classified into two forms: acral PSS (APSS; OMIM 609796) and generalized PSS (OMIM 270300). Although it has been suggested (Traupe, 1989) that the generalized form can be further subdivided into noninflammatory (type A) and inflammatory (type B), other phenotypes including those with hair and nail abnormalities have also been described, further

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complicating the genetics. All three major types present as autosomal recessive conditions and all are characterized by superficial peeling (exfoliation or shedding) of the upper epidermis (Levy and Goldsmith, 1982). Ultrastructural investigation (Brusasco *et al.*, 1998; Hashimoto *et al.*, 2000) indicates that the split occurs between the junction of the stratum corneum and the granular layer (stratum granulosum), focusing recent attention on the processes involved in late epidermal differentiation to explore a molecular explanation for these rare conditions.

APSS

The acral form of peeling skin syndrome, as the name suggests, involves mainly palmar and plantar skin. Genome-wide linkage analysis in two unrelated APSS families (Cassidy *et al.*, 2005) localized the genetic defect to a 10.2-Mb region on chromosome 15 (at 15q15.2). Further fine mapping implicated a small region containing nine genes with a small transglutaminase (TGM) gene cluster (containing TGM5, TGM7, and EPB42) at its center. However, only TGM5 had strong expression in the skin; furthermore, this enzyme was localized to the region between the granular layer and the stratum corneum, precisely where the split occurs in APSS. This enzyme is responsible for introducing γ-glutamyl–ε-lysine isopeptide bonds into the structural proteins (e.g., loricrin, involucrin, small proline-rich proteins) of the cornified envelope and corneocyte. TGM5 spans 33.7 kb of genomic DNA and contains 13 exons, which encode two splice variants. Sequencing of all 13 exons and splice sites revealed the same two homozygous missense mutations (p.T109M and p.G113C) in all affected individuals in both APSS families. However, the molecular pathology appeared to be due solely to the p.G113C mutation, which reduced TG5 enzyme levels to zero (Cassidy *et al.*, 2005). More recently, another report of a Tunisian family with APSS confirmed the involvement of TGM5 gene mutations and another pathogenic variant, a homozygous missense mutation in exon 8 (p.K445N), was identified (Kharfi *et al.*, 2009).

Inflammatory generalized PSS

Detailed studies of inflammatory generalized PSS (type B) followed the success with APSS, but although the pathology was similar and, like APSS, showed certain similarities to Netherton syndrome (NS; Geyer *et al.*, 2005), screening of the TGM5 gene and the gene responsible for NS (SPINK5) revealed no sequence alterations in this condition. Thus, another candidate gene was implicated, and this was revealed using the same technology as for APSS. Whole-genome linkage analysis was performed on a large family with four affected individuals using a chip-based single-nucleotide polymorphism approach (Oji *et al.*, 2010). The histopathology and ultrastructure showed a subcorneal split characteristic of PSS, and genotyping using an Affymetrix GeneChip array (250 K) identified a candidate region on chromosome 6p. Refined mapping produced a LOD score of 5.4 (>3 being significant) to a 5.7-Mb region of DNA at 6p21.3, which contained 195 genes. One of the genes in this region encoded corneodesmosin (CDSN), a specialized component of corneodesmosomes that play an important role in maintaining stratum corneum structural integrity. This seemed an ideal candidate gene and sequencing quickly revealed that all four patients with PSS had the same homozygous missense mutation (p.K59X), resulting in a premature stop codon at the beginning of the transcript. Real-time PCR indicated that 75% of the corneodesmosin mRNA was missing in affected cells, which would ultimately lead to nonsense-mediated mRNA decay. However, there appeared to be little effect on other components of cornified envelope and desmosome formation (e.g., desmocollin 1, desmoglein 1, TGM4, elafin, and LEKTI). Nonetheless, some increase in other proteins was noted (e.g., filaggrin, involucrin, loricrin, and TG1).

Israeli and colleagues confirm the involvement of the CDSN gene in generalized PSS. They studied a four-generation family with a consanguineous union producing two siblings with PSS and three unaffected siblings. Sequencing of the entire CDSN gene including all intron–exon boundaries revealed a homozygous single nucleotide deletion in the center of exon 2 (c.746delG), which caused a premature stop codon 40 bases downstream (p.G249VfsX40). This would truncate the mature protein, which would be missing the whole C-terminal region (about 40% of total length missing). Whether this would cause non-sense-mediated mRNA decay is debatable, but a severely truncated protein would doubtless result.

Noninflammatory generalized PSS

The third major form of PSS is the noninflammatory generalized type A. To date there have been no published molecular genetic studies on families with this condition. Thus, whether defects in TGM5, CDSN, or SPINK5 contribute to this form of PSS is currently unknown and will only become apparent after genome-wide screening of suitable families.

Corneodesmosomes and CDSN

The term corneodesmosome was first proposed 20 years ago in a study to produce monoclonal antibodies to skin proteins (Serre *et al.*, 1991). Human plantar stratum corneum was used to immunize BALB/c mice, and 625 hybridoma supernatants were screened. Several monoclonal antisera to epidermal keratins were identified and two others were reactive with the epidermis, hard palate, and inner root sheath of the anagen hair follicle. One of these antisera (G36-19) showed particular affinity for the stratum granulosum, and immunofluorescence detection indicated the antigen was associated with the cell periphery. Immunogold EM labeling showed a strong association with desmosomes in the granular layer and stratum corneum, whereas immunoblotting showed reactivity to five proteins ranging in molecular weight from 33.5 to 52 kDa. These investigators suggested that the described antigens participated in a corneodesmosome cross-linked envelope superstructure that aided corneocyte cohesiveness.

Two years later, Zhou and Chaplin (1993) identified a skin-associated gene (termed the S-gene) in the HLA class I region. This gene contained two exons and produced two transcripts (2.2

and 2.6 kb) that were associated with differentiating keratinocytes. The proteins had high levels of glycine, serine, and proline and shared some sequence similarity to loricrin and the differentiated keratins (K1 and K10). It became apparent that the product of the S-gene was corneodesmosin, and more extensive studies followed (Simon *et al.*, 1997; Jonca *et al.*, 2002). This protein exists in the extracellular portion of corneocyte desmosomes (corneodesmosomes), and its proteolysis from 52 to 33 kDa is thought to be a prerequisite for the process of desquamation. Corneodesmosin is a basic (p*I* = 8) phosphoprotein that is N-glycosylated and cross-linked to the cornified envelope of corneocytes. It has N-terminal glycine and serine loops similar in structure to those found in loricrin, K1, and K10, which provide homophilic adhesive properties (Caubet *et al.*, 2004).

CDSN and the hair follicle

Corneodesmosin is also found in the inner root sheath of hair follicles, and a 4.2-kb region of upstream sequence was able to direct site-specific expression in both hair follicles and hyperkeratotic epidermis of transgenic mice (Gallinaro *et al.*, 2004). This did not, however, provide sufficient information to direct expression in normal human epidermis. Furthermore, CDSN mutations have been identified in patients with autosomal dominant hypotrichosis simplex (OMIM 146520; Levy-Nissenbaum *et al.*, 2003), and it is curious that similar CDSN gene mutations (p.Q215X and p.Q200X) should produce a different phenotype from the mutations found in PSS (p.K59X and p.G249VfsX40).

One possible explanation is that in the hypotrichosis patients, truncated CDSN aggregates detected in the superficial dermis and hair follicles produced a dominant negative effect on the cells of the hair follicle but little effect on the epidermal corneocytes. One of the PSS mutations (p.K59X) was shown to be susceptible to mRNA decay and in homozygotes would lead to an absence of CDSN, which would appear to be more critical for the corneocyte than the hair follicle. The other PSS mutation causes premature termination much further along the CDSN molecule, may not be susceptible to mRNA decay, and only seems to have a skin phenotype. These complex genotype–phenotype relationships are not uncommon, and more research is required to further understand how specific gene mutations exert their effect.

However, the importance of CDSN to both the epidermis and the hair follicle becomes clear in knockout mice. The use of K14 promoter-driven Cre-mediated *Cdsn* deletion in mice resulted in neonatal death, but grafting of the knockout mouse skin onto nude mice showed that the absence of corneodesmosin resulted in epidermal and hair follicle degeneration and a lethal barrier defect (Leclerc *et al.*, 2009).

CDSN, LEKTI, and NS

As well as an overlap in diagnosis of patients with PSS and NS, there appear to be interactions between the molecules involved in these two conditions. NS is caused by SPINK5 mutations, and this gene encodes a serine protease inhibitor called LEKTI. It appears that in *Spink5*$^{-/-}$ (KO) mice, the lack of LEKTI causes corneodesmosin to undergo premature degradation in the stratum corneum, resulting in epidermal detachment due to desmosomal destabilization (Yang *et al.*, 2004). Thus, some aspects of the phenotype observed in NS are probably a consequence of reduced levels of corneodesmosin, as found in some types of PSS. Israeli and colleagues clearly point this out and also state that they have patients with a similar phenotype that do not appear to have mutations in either CDSN or SPINK5.

CDSN, SPR1, SEEK1, and psoriasis

The PSORS1 locus in the HLA Class I region encompasses two genes on one DNA strand (CDSN, originally called the S-gene, and SPR1) and a single gene (SEEK1) on the opposing strand. Both corneodesmosin and the small proline-rich proteins are directly involved in the late stages of terminal differentiation of the epidermis, but the function of the SEEK1 gene appears less clear. Although this region has shown variable levels of linkage to psoriasis (Tazi-Ahnini *et al.*, 1999; Holm *et al.*, 2003), it is tempting to speculate that alterations in either of the two genes involved in terminal differentiation of the epidermis could modulate the effectiveness of the barrier and the level of cohesiveness between corneocytes in an active psoriatic lesion.

Clinical Implications

- Corneodesmosin (CDSN) mutations have been independently confirmed as the genetic basis of peeling skin syndrome (PSS) type B.
- Patients with PSS type B can now be screened for CDSN mutations, allowing prenatal diagnosis and more effective genetic counseling.
- The structure and function of the corneodesmosome and its importance for maintaining skin integrity and an effective epidermal barrier are now more clearly understood.

Conclusion

Israeli and colleagues' letter confirming that mutations in the corneodesmosin gene are causal in PSS has shed further light on this single structural protein and has provided further insight into the complex relationships between the genotype and phenotype of cutaneous genodermatoses. It also highlights the fact that a single protein can influence the physiology and function of a tissue in different ways.

CONFLICT OF INTEREST

The author states no conflict of interest.

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